Multiscale Modeling of Lung Disease-Influenced Aerosol Dosimetry

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BACKGROUND

- Chronic lung diseases, such as COPD and asthma, are among the leading causes of lost workdays, disabilities, and are the 3rd most prevalent disease-based cause of death in the U.S. COPD is generally associated with exposure to toxic/irritant aerosols.
- The lungs have also been used as a potential route for local and systemic delivery of therapeutic aerosols for diseases where drugs may not be as effective by other routes of administration.
- As a result, the development of predictive aerosol dosimetry models has been a major focus of environmental toxicology and pharmaceutical health research for decades. However, to date, the challenge of predicting the deposition of inhaled aerosols under disease conditions is largely unmet.

OBJECTIVES

- Develop a multi-scale, computationally efficient framework to accurately predict site-specific aerosol deposition patterns for both normal and diseased lungs. The framework will explicitly incorporate
  - heterogeneities in airway anatomy and tissue mechanics, respiratory behavior and physiology,
  - interactions between airflow and aerosol physics.
- Year 1 objective:

  To bi-directionally couple 3D-CFD models of upper and large airways with 1D Navier-Stokes airflow and particle transport models based on the Multiple Path Particle Deposition (MPPD) Model.

Bi-Directional Coupling of 3D-1D Airflow Models

$$P_i - P_{i-1} = R_i Q_i + L_i \frac{dQ_i}{dt} \qquad Q_{i+1} - Q_i = C_i \cdot \frac{d}{dt}\left(P_i - P_{PL}\right)$$

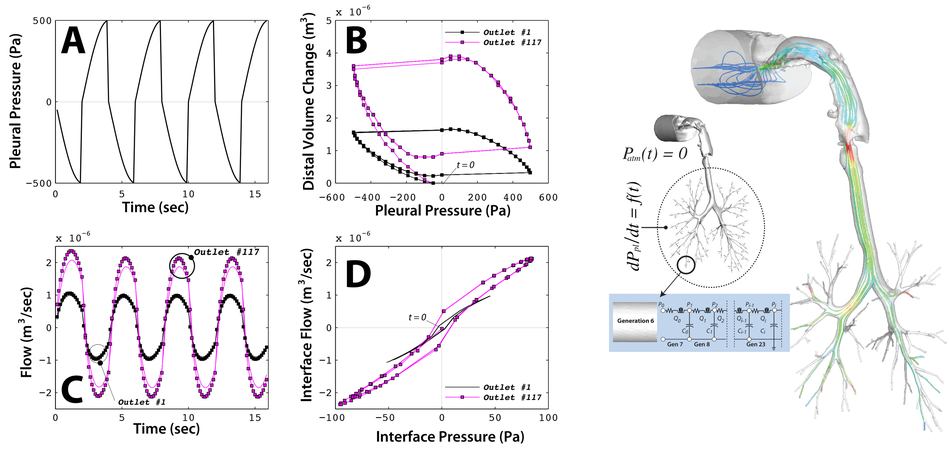
$$R_i^t = R_i^{t=0}\left(\frac{A_i^{t=0}}{A_i^t}\right)^2 \qquad L_i^t = L_i^{t=0}\left(\frac{A_i^{t=0}}{A_i^t}\right)$$

$$dV_i = \left(Q_{i+1} - Q_i\right)\Delta t \qquad dA_i = dV_i / \left(l_i \cdot 2^{t-t_0-1}\right) \qquad A_i^t = A_i^t + dA_i$$

3D Airways

$$P_{alv} - P_{term} = R_{alv} Q_{alv} \qquad -Q_{alv} = C_{alv} \cdot \frac{d}{dt}\left(P_{alv} - P_{PL}\right)$$

1D Airways

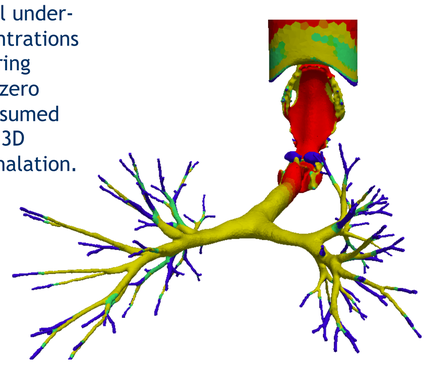


- Airflow transferred conservatively between 3D and 1D domains at each distal outlet
  - 1D domains represented by RLC models that reflect airflow, pressure, and tissue mechanics
- Inner iteration used to arrive at appropriate time-dependent pressures at interface between the 1D and 3D domains
- NACCEL procedure speeds up inner iteration so cost of running combined code is similar to running uncoupled 3D model. (Kuprat et al., *J. of Comput. Physics, 2013.* ***244****:148-167)*

Bi-Directional Coupling of 3D-1D Airflow & Aerosol Models

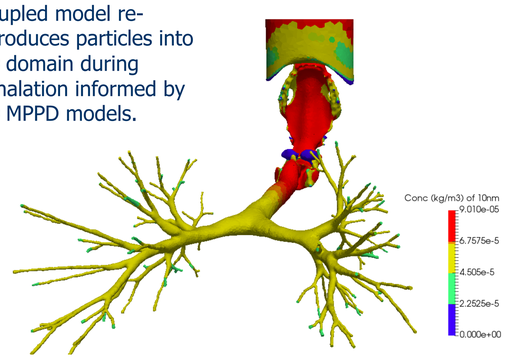
Human 3D Geometry without distal MPPD models

Uncoupled model under-estimates concentrations in 3D domain during expiration since zero concentration assumed at distal ends of 3D model during exhalation.



Human 3D Geometry with117 distal MPPD models

Coupled model re-introduces particles into 3D domain during exhalation informed by 1D MPPD models.



Particle concentrations shown just after beginning of expiratory airflow.

- Particle mass transferred between 3D domain and distal 1D at each of 117 distal outlets
  - Convection-diffusion equation used in 3D domain for small (10 nm) particles
  - Multiple Path Particle Deposition model (MPPD) used in 1-D domains *(Anjilvel, S. and B. Asgharian. Fundamental and Applied Toxicology, 1995.* ***28****:41-50; Asgharian, B., et al. Aerosol Science and Technology, 2001.* ***34****:332-339).*
  - Airflow & particle mass conserved between models

CONCLUSIONS AND NEXT STEPS

- Bi-directionally coupled 3D-1D model predicts ventilation heterogeneities & aerosol transport & deposition profiles not predicted by 3D or 1D models alone.
- Incorporation of 1D MPPD model critical for accurate 3D-CFD simulations of particle fate during exhalation.
- Next steps:
  - Develop more efficient Eulerian & Lagrangian transient 3D simulation approaches for wide range particle sizes.
  - Evaluate model performance against our rich database of multi-modal 3D imaging and aerosol deposition measurements in human volunteers that include both healthy and COPD cohorts.

MODEL CREDIBILITY PLAN

- Biological Basis:
  - Structural verification/biological fidelity: Does the model specifically address key processes known to be important to the application?
  - Parameter verification: Is the source for each model parameter clearly identified and documented? Are data used to estimate model parameters independent of data used for model evaluation?
- Computational Basis:
  - Mathematical verification: Does the model produce correct and reproducible results? Are the equations appropriate for the process being described? Are the model codes devoid of errors? Are integration algorithms and associated precision appropriate and specified?
  - Computational implementation: Have the simulations appropriately converged and are results mesh-independent for CFD simulations? Is the model mass, flow and energy balanced? Are results comparable across platforms? Are all boundary conditions reported?
- Model Reliability:
  - Model variability vs. uncertainty: How sensitive are model simulations to choices in parameter estimates? How variable are experimentally determined model parameters and how does this variability affect simulation results?
  - Model evaluation: How well do model predictions compare with experimental results? Are experimental data and CFD-based simulation comparisons at the same level of resolution? And when they are not, is that explicitly addressed?

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